

Remarks

Amendments in Response to the Final Office Action Mailed October 22, 2003

Independent claims 66, 88, and 92 as amended recite that the live *P. haemolytica* bacterium “when in a suitable physiological environment” expresses the recited mutant leukotoxin molecule. This amendment is supported *inter alia* on page 13, lines 4-6: “A new protein of approximately 65 kDa was detected in the culture supernatant of this mutant by SDS-PAGE, consistent with the predicted molecular weight of the deleted product.”

New dependent claims 96-100 recite that the live bacterium is lyophilized (claims 96, 98, and 100) or reconstituted from a lyophilized preparation (claims 97, 99, and 101). These dependent claims are supported on page 4, lines 14-15: “The bacteria in the vaccine formulation can be live, lyophilized, lyophilized and reconstituted, or killed.”

Independent claims 81, 91, and 95 have been amended to recite “a vaccine formulation” that comprises “at least two sources of a form of a leukotoxin molecule, wherein the form of the leukotoxin molecule is a deletion mutant of about 66 kDa which lacks amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin, wherein the first source is a killed *P. haemolytica* bacterium, wherein a live form of the killed bacterium (a) expresses no biologically active leukotoxin, (b) expresses the form of the leukotoxin molecule, and (c) contains no non-*P. haemolytica* DNA, and wherein the second source comprises the form of the leukotoxin molecule.” New dependent claims 102-104 recite that the second source of the form of a leukotoxin molecule is selected from the group consisting of purified protein, a bacterial lysate, a bacterial extract, and a culture supernatant.

The amendment and the new claims are supported on page 4, lines 15-17: “Moreover, bacterial lysates, extracts or culture supernatants which contain the LtkA deletion protein can be used in the vaccine formulation. Purified protein can also be used, if desired.”

Applicants have deleted more claims (claims 67-80, 89, 90, 93, and 94) than those added by this amendment. The new claims and amendments were not presented previously because Applicants believed the arguments in the last response were sufficient to overcome the rejection. The amendments do not recite new subject matter and do not require a new search. The new dependent claims recite subject matter previously recited in canceled independent claims. The new dependent claims clarify the claimed subject matter by indicating that “lyophilized” bacteria and bacteria “reconstituted from a lyophilized preparation” are species of “live” bacteria. The amendments also present the claims in better form for appeal.

Amendments in Response to the Advisory Action Mailed May 7, 2004

The Advisory Action mailed May 7, 2004 stated that the amendments filed in response to the Final Office Action were not entered because they “raise new 112, second paragraph issues that would require further consideration and search.” Advisory Action at page 2, paragraph no. 2. The Advisory Action suggested several amendments intended to expedite the claims to allowance.

As suggested in the Advisory Action, independent claims 66, 88, and 92 have been amended to recite a “suitable” physiological environment. Claims 81, 91, and 95 have been amended to recite the first source and the second source.

The Advisory Action also suggested that the Markush group of new claims 102-104 be recited in independent claims 81, 91, and 95, respectively to avoid raising new issues under 35

U.S.C. § 112, second paragraph. Applicants have not made this amendment. The second paragraph of 35 U.S.C. § 112 states that:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

It is well settled that a claim must “reasonably apprise those skilled in the art both of the utilization and scope of the invention.” *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 134-38, 118 U.S.P.Q. 122, 130 (2d Cir. 1958), *cert. denied*, 358 U.S. 884 (1958). Independent claims 81, 91, and 95 meet this standard.

Those skilled in the art would not find the recitation of a second source of the recited leukotoxin molecule to be indefinite. The specification teaches four examples of the recited second source (*i.e.*, those recited in dependent claims 102-104). Provided with these four examples, those of skill in the art at the December 6, 1993 priority date of this application would have understood that the recited form of the leukotoxin molecule also could be obtained from other sources, such as eukaryotic cells engineered to express the recited molecule. In light of this understanding, it would be unduly narrowing to require amendment of claims 81, 91, and 95 to recite only four second sources of the recited leukotoxin molecule.

Applicants respectfully request entry of the amendments and the new dependent claims.

The Obviousness-Type Double Patenting Rejections of Claims 36-41 and 66-95

Claims 36-41 and 66-95 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-9 of U.S. Patent 6,495,145 and claims 22-29 of co-pending application Serial No. 09/736,169.

Claims 67-80, 89, 90, 93, and 94 have been canceled. To expedite prosecution of the remaining claims, a Terminal Disclaimer under 37 C.F.R. § 1.321 over claims 1-9 of U.S. Patent 6,495,145 was filed March 22, 2004. Serial No. 09/736,169 is abandoned; a non-final rejection to which Applicants did not respond was mailed in that application on December 4, 2002. Thus, no terminal disclaimer over Serial No. 09/736,169 is needed.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 66-95 Under 35 U.S.C. § 112, second paragraph

Claims 66-95 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 67-80, 89, 90, 93, and 94 have been canceled. Applicants respectfully traverse the rejection of claims 66, 81-88, 91, 92, and 95.

The second paragraph of 35 U.S.C. § 112 states that:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

It is well settled that a claim must “reasonably apprise those skilled in the art both of the utilization and scope of the invention.” *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 134-38, 118 U.S.P.Q. 122, 130 (2d Cir. 1958), *cert. denied*, 358 U.S. 884 (1958). Claims 66, 81-88, 91, 92, and 95 meet this standard.

The Final Office Action asserts that claims 81-87, 91, and 95 are be vague and indefinite because claim 81 recites that a killed bacterium is administered to the ruminant. The Final Office Action requests clarification of how a vaccine preparation comprising the recited killed bacterium differs from a vaccine preparation comprising a killed wild-type *P. haemolytica*. Independent claims 81, 91, and 95 have been amended to recite a vaccine formulation that contains the mutant leukotoxin protein as well as the killed bacterium. Thus, at least one difference between the claimed vaccine formulation and a vaccine formulation comprising a killed wild-type *P. haemolytica* is that the claimed vaccine formulation contains the mutant leukotoxin protein.

The Final Office Action asserts that claims 67-80, 90, 93, and 94 are vague and indefinite because “it is unclear what is meant by administering a ‘lyophilized’ . . . versus a ‘lyophilized and reconstituted’ . . . *P. haemolytica* vaccine.” Final Office Action at page 3, first full paragraph. Claims 67-80, 90, 93, and 94 have been canceled. Similar subject matter, however, is recited in new dependent claims 96-101. New dependent claims 96, 98, and 100 recite that the live bacterium of claim 66 is lyophilized. New dependent claims 97, 99, and 101 recite that the live bacterium of claim 66 is “reconstituted from a lyophilized preparation.”

The term “lyophilized” is well known in the art and means “freeze-dried.” Lyophilization is a common method of preserving a live bacterial vaccine until it is administered. *See, e.g.*, the abstract of Confer *et al.*, *Am. J. Vet. Res.* 47, 1853-57, 1986 (Attachment 1 to the response filed March 22, 2004). Those skilled in the art understand that a live bacterium reconstituted from a lyophilized preparation means that the recited live bacterium was lyophilized but has now been placed in a suitable liquid medium in which the live bacterium can

function. *Id.*: “Lyophilized *P. haemolytica* was reconstituted and used as a live vaccine in 3 experiments.”

The Final Office Action requests clarification of how a lyophilized bacterium “would not degrade while sitting on animal feed.” The Final Office Action also states it is unclear “how a dry powder of a lyophilized bacterium would allow for the active ingredient, the modified leukotoxin, to be expressed in the ruminant.” Final Office Action at page 3, first full paragraph.

First, whether some amount of dry lyophilized bacteria “degrade while sitting on animal feed” is not relevant to whether or not the claims are definite because the claims recite no time period during which the recited bacteria must not degrade. Second, bacteria in lyophilized preparations are still “live.” Lyophilized live bacteria administered dry, for example as top-dressing on feed, become reconstituted in the animal. When the dry, lyophilized bacteria come in contact with a moist environment in a ruminant (*e.g.*, an oral, pharyngeal, or nasal surface), it will become wet and reconstituted. The reconstituted bacteria can multiply on the host mucosa and can express the mutant leukotoxin. See paragraphs 22 and 23 of the declaration of Dr. Briggs filed March 22, 2004, which describes a field trial in which lyophilized bacteria were top-dressed on feed. Administration of dry lyophilized live bacteria in this manner “dramatically reduced nasal colonization by virulent *M. haemolytica* serotype 1 ($p < 0.001$).” Paragraph 23 of the declaration. Thus, dry lyophilized live bacteria do allow for the active ingredient, the modified leukotoxin, to be expressed in the ruminant.

The Final Office Action asserts that claims 74, 90, and 94 are vague and indefinite because these claims recite that the bacterium is reconstituted prior to administration. Claims 74, 90, and 94 have been canceled; however, similar subject matter is recited in new dependent claims 97, 99, and 101. As explained above, “reconstituted” simply means that the lyophilized

bacteria are placed into a suitable liquid before being administered to a ruminant. As the Final Office Action notes, the claims encompass reconstitution in adjuvant as well as reconstitution in growth medium.

The Final Office Action also questions how administration of a lyophilized and reconstituted bacterium differs from administration of a lyophilized bacterium. A lyophilized bacterium is a dry, freeze-dried bacterium; a reconstituted bacterium is wet (*i.e.*, is in a liquid). *See Confer et al.* (Attachment 1 to the response filed March 22, 2004).

Claims 66, 81-88, 91, 92, 95, and new dependent claims 96-101 are clear and definite because they reasonably convey to one skilled in the art what the invention is. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 67-87, 89-91, and 93-95 Under 35 U.S.C. § 112, first paragraph

Claims 67-87, 89-91, and 93-95 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Claims 67-80, 89, 90, 93, and 94 have been canceled. Applicants respectfully traverse the rejection of claims 81-87, 91, and 95.

The Final Office Action acknowledges that claims to methods of inducing immunity using live forms of the bacterium recited in claim 66, as well as claims to vaccines and feeds comprising the bacterium, are enabled. Yet the Office Action questions the enablement of similar claims (now canceled but replaced with claims with the same recitations) that recite lyophilized, lyophilized and reconstituted, or killed bacteria.

Use of lyophilized bacteria or lyophilized and reconstituted bacteria

The pending claims have been amended to clarify that lyophilized bacteria and bacteria reconstituted from lyophilized preparations are species of live bacteria. The declaration of Dr.

Robert Briggs filed March 22, 2004 describes four field trials in which both types of vaccines (containing dry, lyophilized bacteria and containing bacteria reconstituted from a lyophilized preparation) were administered to ruminants and proved effective in inducing immunity to pneumonic pasteurellosis. In each trial, the bacterial strain in the vaccines was D153ΔlktA34-378; these are *P. haemolytica* that do not express a biologically active leukotoxin, express a mutant leukotoxin protein that lacks amino acids 34-378, and contain no non-*P. haemolytica* DNA. The collective results of the four trials demonstrates that such bacteria, whether administered dry or reconstituted, induce immunity to pneumonic pasteurellosis as measured by reduced mortality, increased serum antibody titers against *P. haemolytica*, or reduced nasal colonization by *P. haemolytica*.¹

Paragraphs 4-7 and 11-21 of the declaration describe two field trials in which bacteria reconstituted from a lyophilized preparation were top-dressed on feed. In one trial, the calves to which the bacteria were administered gained weight and had reduced mortality (4% of the population vs 16% of the unvaccinated population) from *M. haemolytica* infection. See paragraphs 4-7 of the declaration. In another trial, the calves to which the bacteria were administered had increased serum antibody titers against *M. haemolytica* and increased weight gain when compared with unvaccinated animals. See paragraphs 11-21 of the declaration.

Paragraphs 8-10 of the declaration describe a field trial in which bacteria reconstituted from a lyophilized preparation were administered intranasally. The calves to which the bacteria were administered had increased serum antibody titers against *M. haemolytica* and increased weight gain when compared with unvaccinated calves.

¹ Since this application was filed, *P. haemolytica* has been renamed "*Mannheimia haemolytica*." The declaration uses the new terminology.

Paragraphs 22 and 23 of the declaration describe a field trial in which lyophilized bacteria were top-dressed on feed and administered to calves. Administration of dry lyophilized live bacteria in this manner “dramatically reduced nasal colonization by virulent *M. haemolytica* serotype 1 ($p < 0.001$).” Paragraph 23 of the declaration.

The results of the trials described in Dr. Briggs’ declaration demonstrate that vaccines containing lyophilized live bacteria and reconstituted, previously lyophilized live bacteria work as described in the specification.

Use of vaccine formulations containing killed bacteria

Independent claims 81, 91, and 95 as amended to recite a vaccine formulation that comprises at least two sources of a form of a leukotoxin molecule; the form of the leukotoxin molecule is a deletion mutant of about 66 kDa which lacks amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin. The first source is a killed *P. haemolytica* bacterium, wherein a live form of the killed bacterium (a) expresses no biologically active leukotoxin, (b) expresses the form of the leukotoxin molecule, and (c) contains no non-*P. haemolytica* DNA. The second source comprises the form of the leukotoxin molecule. The claimed vaccine preparation contains an active agent (the leukotoxin deletion mutant protein) that the specification teaches is useful as a vaccine. Specification at page 3, line 15 to page 4, line 31.

Vaccine preparations containing a killed bacterium (bacterin) and an inactivated protein toxin (toxoid) for inducing immunity against *P. haemolytica* were well known in the art at the priority date of this application (September 25, 1997). See Srinand *et al.*, *Vet. Microbiol.* 49, 181-95, 1996 (Attachment 2 to the response filed March 22, 2004); and Confer, *Vet. Microbiol.* 37, 353-68, 1993 (Attachment 3 to the response filed March 22, 2004). Thus, those of skill in

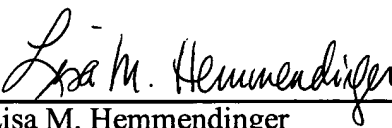
the art at that time knew how to make and use such preparations to induce immunity against *P. haemolytica*. In fact, such bacterin-toxoid preparations are still commercially available (e.g., "One Shot," referred to in Srinand *et al.*, above).

The specification, together with the skill in the art at the priority date of this application, enables making and using vaccines containing the recited live, lyophilized live, and reconstituted lyophilized live bacteria, as well as vaccines containing the recited killed bacteria and leukotoxin mutant protein. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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